49. Endocrine Effects in the Brain and Their Relationship to Behavior

Bruce S. McEwen

50: MOLECULAR BASIS OF LEARNING AND MEMORY

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Brief History of Memory Research: The Penfield Studies

Amnesia in H.M. and Temporal Lobe

Declarative Memory vs. Procedural Memory

Short-Term Memory vs. Long-Term Memory

Hebb's Rule and the NMDA receptor

Long-Term Potentiation

Long-Term Depression

Molecular Switch of Learning

Molecular Basis of Long-Term Memory

Systems Level of Memory Consolidation and Storage

Learning and Memory Enhancement

52. NEUROBIOLOGY OF SEVERE MOOD AND ANXIETY DISORDERS

John J Mann & Husseini K Manji

MOOD DISORDERS

- INTRODUCTION
- MORBIDITY AND MORTALITY
- DEPRESSION AND BIPOLAR DISORDER ARISE FROM INTERACTIONS BETWEEN SUSSCEPTIBILITY GENES AND ENVIRONMENTAL FACTORS
- MULTIPLE NEUROTRANSMITTER AND NEUROPEPTIDE SYSTEMS ARE IMPLICATED IN THE PATHOPHYSIOLOGY AND TREATMENT OF MOOD DISORDERS
  - Serotonergic System
  - Noradrenergic System
  - Dopaminergic System
  - Cholinergic System
  - Glutamatergic System
  - GABAergic System
  - CRH/HPA Axis
  - Other Neuropeptides
- ABNORMALITIES OF CIRCADIAN AND OTHER RHYTHMS
- NEUROANAMTOMICAL AND NEUROPATHOLOGIC CORRELATES OF MOOD DISORDERS
- STRESS & GLUCOCORTICOIDS MODULATE NEURAL PLASTICITY: IMPLICATIONS FOR SEVERE MOOD DISORDERS
- SIGNALING PATHWAYS ARE INVOLVED IN THE PATHOPHSYIOLOGY AND TREATMENT OF SEVERE MOOD DISORDERS
  - ❖ cAMP Generating System

next page

- ❖ Phosphoinositide/PKC Signaling Cascade
- ❖ Wnt Signaling Cascade
- ❖ Neurotrophic Signaling Cascades

ANXIETY DISORDERS

- INTRODUCTION AND CLASSIFICATION

- ANIMAL MODELS OF FEAR/ANXIETY
  Issues of Validity of Models

- GENETIC STUDIES OF ANXIETY IN MICE

- NEUROCHEMISTRY OF FEAR AND ANXIETY

  - ❖ Noradrenergic System
  - ❖ Serotonergic System
  - ❖ GABAergic System
  - ❖ Neurosteroids
  - ❖ CRF and the Stress Axis
  - ❖ NPY & other Neuropeptides
  - ❖ Intracellular Cascades

- CONCLUDING REMARKS: FUTURE DIRECTIONS & THE DEVELOPMENT OF NOVEL THERAPEUTICS

- REFERENCES

- ADDITIONAL REFERENCES

ADDICTION

Marina Wolf

I. Basic definitions

A. Addiction: compulsive drug craving and administration despite tremendous adverse consequences
B. Tolerance: The need for an increasing dose of drug to achieve the same effect
C. Sensitization: Enhancement of some drug responses as a result of repeated drug exposure
D. Dependence: Physical dependence refers to an altered physiological state resulting from repeated drug exposure, such that cessation of drug use leads to a somatic withdrawal syndrome. Psychological dependence refers to emotional or motivational symptoms that follow drug withdrawal. Depending on the drug in question, both physical and psychological dependence can contribute importantly to compulsive drug craving.

II. Natural reinforcers and drugs of abuse use similar circuitry

A. Early theories of behavior emphasized importance of reducing aversive states, e.g., reinforcers such as eating or drinking can shape behavior because they reduce aversive states (hunger and thirst). Current theories emphasize the ability of rewards to act as incentives, causing neural representations that elicit motivation and pursuit of goals.
B. Drugs of abuse "usurp" neural circuits that mediate incentive value of natural reinforcers, so studying neurobiology of natural reinforcers is important for understanding addiction.
C. The major substrate for natural reward is the mesocorticolimbic dopamine (DA) system (*Fig. 1: reward circuits*). Most research focuses on DA neurons in ventral tegmental area (VTA) that project to the nucleus accumbens (ventral striatum). Nucleus accumbens neurons receive inputs from limbic and cortical regions that convey motivational information; they project to motor regions. Hence, nucleus accumbens has been described as an interface between limbic and motor systems, where motivation is converted to action. However, DA neurons in the substantia nigra, which project primarily to dorsal striatum, also participate in reward circuitry. Recent work has focused on their role in the performance of habitual behaviors associated with addiction.
D. Natural rewards activate these midbrain DA neurons. So do all drugs of abuse, but different drugs have different targets in brain and thus use different mechanisms to activate DA neurons. Psychostimulants directly increase DA transmission by blocking DA uptake and/or promoting release, while opiates, nicotine and ethanol do so indirectly by interacting with other transmitter systems that regulate DA cell activity. Three important transmitters for regulation of DA cell activity at the level of the VTA are glutamate, GABA and acetylcholine [*Fig. 2 will show important inputs/mechanisms regulating VTA DA cell activity, and illustrate how various addictive drugs tap into these mechanisms]*.
E. What is the actual role of DA in mediating reinforcement? Originally, DA was suggested to mediate the pleasure evoked by rewarding stimuli, but it was shown in 1980's that animals lacking DA, due to lesions, still emitted responses indicating that they "liked" or "didn't like" particular tastes. Accordingly, two major current theories:

Next page

1. DA neurons "learn and predict" the occurrence of rewards, and thus participate in the ongoing learning of adaptive behaviors (Schultz, DiChiara). Fits well with ability of DA (and drugs of abuse) to promote stimulus/reward learning on a behavioral level and modulate neuronal plasticity on a cellular level.
2. DA neurons attribute incentive salience to rewards and to conditioned stimuli associated with rewards, enhancing the extent to which they are "wanted" and can therefore shape behavior (Robinson and Berridge). This theory has spawned the useful adage that DA mediates "wanting" not "liking". Repeated administration of drugs of abuse is proposed to sensitize the DA-dependent systems that mediate incentive salience, leading to pathological intensification of drug "wanting".
3. Both theories help explain how chronic drug exposure facilitates the formation of new habits that center around drug-seeking behavior, usually at the expense of more appropriate behaviors. They also help explain the powerful ability of drug-related cues to drive drug-seeking behavior and promote relapse even after long periods of abstinence.

F. While these theories are important, addiction cannot be conceptualized simply as an enhancement of DA-regulated incentive-motivational processes.
   1. The desire to overcome aversive effects associated with withdrawal may also contribute to compulsive drug-seeking in addicts, particularly in the short run.
   2. Addiction is characterized by cognitive dysfunction (impulsivity, loss of behavioral inhibition) as well as motivational dysfunction.
   3. Altered stress responses contribute to addiction. Repeated drug exposure increases vulnerability to stress, and stress is a powerful trigger for drug-taking in addicts and relapse in recovering addicts. A common element of withdrawal syndromes produced by several drugs of abuse is elevation of CRF levels in the mesolimbic system, which may mediate stress-like symptoms of withdrawal.
   4. Individuals differ greatly in their vulnerability to drugs of abuse – this is a topic of intense research.

G. The role of DA neurons in reward/addiction has to be studied within the context of the complex neuronal circuits within which the DA neurons are embedded. Many reciprocal connections exist between limbic, cortical and motor regions (*see Fig. 1*). Important points to make:
   1. A general rule is that neurons receiving DA inputs (e.g., nucleus accumbens neurons) also receive convergent glutamate and GABA inputs. These inputs are the primary determinants of neuronal excitability. DA plays a modulatory role, albeit a critical one, by influencing synaptic transmission and modulating voltage-dependent conductances.
   2. After chronic drug administration, many important adaptations occur downstream of DA neurons, and involve multiple transmitter and signal transduction systems.

II. Classes of Addictive Drugs

A. Stimulants (cocaine and the amphetamines)
   1. Cocaine, amphetamine, methamphetamine, MDMA, methylphenidate: Behavioral effects, addictive potential, withdrawal syndrome

Next page

2. Initial targets in brain: monoamine transporters (DAT, SERT, NET). Different stimulants interact differently with transporters. Cocaine is a monoamine uptake inhibitor. Amphetamine and its derivatives are competitive inhibitors of monoamine uptake but also substrates for monoamine transporters; through the latter mechanism they promote DA efflux by reverse transport. They also promote redistribution of DA from synaptic vesicles to the cytosol by collapsing vesicular pH gradient (weak base mechanism). Very recent studies suggest that amphetamine can also cause DAT internalization, a novel mechanism for regulating DA uptake. Different stimulants differ somewhat in relative affinities for DAT, SERT and NET. Amphetamine – almost equal affinities for DAT and NET, lower for SERT. Cocaine: higher for SERT and DAT then NET. Interaction with DAT is most critical for rewarding effects of cocaine but SERT also plays a role. Methamphetamine: DAT > SERT. MDMA: DAT and SERT about equal. Methylphenidate (Ritalin) – highest at DAT.
3. New ideas in stimulant research:
    i. MDMA and METH lead to permanent impairments of memory/impulsivity that are linked to their neurotoxic effects on serotonin systems.
    ii. Methylphenidate (Ritalin) exposure may enhance reactivity and vulnerability to other drugs of abuse, e.g. cocaine, later in life. The implications of this are quite serious as Ritalin is widely prescribed for treatment of attention deficit hyperactivity disorder (ADHD), the most commonly diagnosed disorder of childhood.
4. Mechanisms of stimulant action: Blockade of monoamine transporters enhances monoamine transmission – increased DA transmission most closely linked to rewarding effects. I will briefly review DA receptor subtypes unless this is covered elsewhere in the book (??). D1 and D2 receptors play key roles. D1 receptors are positively coupled to adenylyl cyclase, D2 receptors are negatively coupled. Through the cAMP-PKA pathway, DA receptor signaling influences cellular targets that regulate neuronal excitability (e.g., ligand and voltage-gated ion channels) as well as targets that contribute to long-term adaptations (transcription factors such as CREB). [*I will expand on this section with the help of a diagram – Fig. 3 - that will include DARPP32, cdk5, etc, and also illustrate possible interactions with glutamatergic signaling – based on similar diagrams in Greengard's reviews*].
5. Long-term adaptations involve a cascade of changes involving different transmitter systems and different brain regions at different withdrawal times. Shortly after discontinuing stimulant administration, DA neurons are hyperexcitable due to several mechanisms, possibly including LTP at glutamate synapses onto DA neurons. This is transient, but serves to trigger longer-lasting changes in downstream pathways. For example, changes in glutamate transmission occur throughout the mesocorticolimbic system. AMPA transmission in the nucleus accumbens seems particularly important in driving cocaine-seeking behavior in rats. On a cellular level, upregulation of the D1-cAMP-PKA-CREB pathway in nucleus accumbens may play a role in some adaptations. Prolonged D1 receptor activation increases expression of dynorphin,

Next page

an endogenous opioid peptide encoded by a CREB-regulated gene. Dynorphin binds to _ opioid receptors on DA nerve terminals, producing a decrease in DA release that may contribute to dysphoria during withdrawal.

B. Opiates

1. Opium, extracted from poppy plants, has been used for recreational and medicinal purposes for thousands of years. Morphine identified as active pharmacological ingredient in early 1800's. Heroin synthesized from morphine in late 1800s in attempt to develop non-addicting cough suppressant. Heroin is more lipophilic than morphine, therefore produces effects more rapidly. The term "opioid" is more inclusive, encompassing natural derivatives of opium such as morphine, synthetic morphine-like drugs including heroin, and the endogenous opioid peptides (endorphins, endomorphins, enkephalins, dynorphins).
2. Acute behavioral actions: analgesia, autonomic inhibition and "high". All effects show tolerance. Severe withdrawal syndrome, with physical and psychological components. The mesocorticolimbic system is important for acute rewarding effects and psychological withdrawal symptoms/craving. Opiate actions in spinal cord and brain stem are responsible for analgesic and autonomic effects of opiates and bulk of physical withdrawal symptoms – a particularly important area for physical withdrawal syndrome is the locus coeruleus (LC), the major noradrenergic nucleus in brain. Located in the brainstem, the locus coeruleus regulates autonomic function and attentional states.
3. Initial targets in brain: three opioid receptor types (_,_,_). The _-opioid receptor is critical for rewarding effects of opioids. Generally mediates neuronal inhibition (briefly review signal transduction pathways). Effects in VTA and nucleus accumbens are particularly important. In VTA, opioids activate DA neurons through an indirect mechanism – they stimulate _-opioid receptors on VTA GABA neurons that synapse on VTA DA neurons. This inhibits the GABA neurons, leading to disinhibition of the DA neurons and DA release in NAc and other target areas (Fig. 1). Opiates also directly affect NAc neurons independently of dopamine by activating opioid receptors on the NAc neurons themselves. Relative contribution of these two sites of action to rewarding effects of opiates is still not clear. There is increasing evidence that endogenous cannabinoid systems are also important in mediating the rewarding effects of opiates and vice versa.
4. Neurobiology of physical withdrawal syndrome: During chronic opiate administration, LC neurons develop tolerance to acute inhibitory effects of opiates, so upon removal of opiates (withdrawal) they exhibit a dramatic rebound increase in activity. This increase in NE transmission is responsible for many withdrawal symptoms. A cellular mechanism that contributes importantly to rebound activation of LC neurons has been worked out (one of first addiction-related mechanisms to be understood at cellular/signal transduction level; Nestler). Opiates inhibit LC neurons in part through inhibition of adenylyl cyclase (which leads to inhibition of a nonspecific cation current). During chronic opiate administration, expression of adenylyl cyclase and PKA in the LC is increased, which increases the excitability of the neurons, enabling them to return to normal

Next page

firing rates despite continued presence of opiates. When drug is withdrawn, up-regulation of the cAMP pathway is no longer opposed by inhibitory effects of opiates, leading to abnormally high firing rates of LC neurons.

5. Craving and psychological dependence: In nucleus accumbens, chronic opiate treatment leads to downregulation of _-opioid receptors and upregulation of cyclic AMP-PKA pathway, increasing CREB-mediated dynorphin transcription. Dynorphin stimulates presynaptic _ receptors on DA nerve terminals, inhibiting DA release and contributing to dysphoria. Note that upregulation of cAMP-PKA-CREB signaling also implicated in adaptive responses to chronic stimulant administration (above). In addition, adaptations in CRF neurons may contribute to anxiety of withdrawal and vulnerability to stress-induced relapse.
6. Two main treatments for opiate withdrawal syndrome: 1) replacement therapy with methadone or other _ agonists – longer half-life than heroin or morphine, produce mild stimulation rather than euphoria. Also produces cross-tolerance to heroin, lessening its effect if patients relapse. 2) _2 agonist clonodine (many autonomic effects of opiate withdrawal are due to loss of opioid inhibition of NE neurons).

C. Phencyclidine (PCP, angel dust)
    1. A dissociative anesthetic, similar to ketamine. Produces powerful euphoric effects as well as dysphoric effects in humans. PCP and ketamine mimic both positive and negative signs of schizophrenia in humans.
    2. Mechanism of action: long known to be a weak DA uptake blocker, but more recently it has been established that its major mechanism of action involves noncompetitive antagonism of NMDA-type glutamate receptors. This realization, coupled with its ability to mimic schizophrenic symptoms, was an important impetus for glutamate-based theories of the pathogenesis of schizophrenia (is this covered elsewhere in the book? – if so, I won't say too much about PCP in the addiction chapter). PCP can activate DA neurons indirectly, through blockade of NMDA receptors that influence DA neuron activity, but many of its actions related to rewarding effects appear to be dopamine-independent. Also produces neurotoxicity through NMDA receptor blockade.

D. Marijuana (cannabinoids)
    1. Derivatives of *Cannabis Sativa L.*, such as marijuana and hashish, have been used for centuries for recreational and therapeutic purposes. Rapid progress in recent years due to:
        i. Cloning of G-protein coupled receptors for cannabinoids (CB1 in brain, CB2 in periphery), development of increasingly specific antagonists for these receptors, and development of CB1 and CB2 knockout mice
        ii. Identification of endogenous cannabinoids (endocannabinoids), synthetic and hydrolyzing enzymes for cannabinoids, and transporters for cannabinoids – these have been used to define cannabinoid-utilizing brain pathways.
    2. The psychoactive component of cannabis is Δ^9tetrahydrocannabinol (THC). THC, as well as cannabimimetics and endocannabinoids, mediate their actions in

Next page

the central nervous system through CB1, a Gi/Go-protein coupled receptor that is widely distributed in brain and has been shown to inhibit adenylate cyclase, activate MAP-kinases, reduce Ca^{++} currents, and modulate several K^{+} conductances. Activation of CB1 receptors inhibits synaptic transmission in many brain regions.

3. Behavioral effects: Acute effects in humans include euphoria, giddiness, relaxation, sedation and sometimes anxiety, paranoia and panic. Abrupt cessation of heavy marijuana use can produce a cannabinoid withdrawal syndrome characterized by drug craving restlessness, irritability, agitation, insomnia, nausea and cramping. Initially, behavioral studies of cannabinoids in animals were complicated by difficulty in demonstrating rewarding effects in common animal models, due to prominent aversive effects at higher doses. However, direct reinforcing properties are now established, as well as tolerance and dependence.
4. Neurobiological basis of reinforcing effects of cannabinoids: Mediated by CB1 receptors but involve actions on multiple systems. Regulation of mesolimbic DA system is important. In VTA, cannabinoids activate presynaptic CB1 receptors that inhibit GABA release, which disinhibits the DA neurons. In the nucleus accumbens, cannabinoids also activate presynaptic CB1 receptors that depress glutamate and GABA release. There may also be postsynaptic interactions between DA receptors and CB1 receptors. In addition to DA systems, endogenous opioid systems play an important role in reinforcing effects of cannabinoids, as opioid antagonists block cannabinoid self-administration in monkeys and rodents. This interaction between cannabinoids and opioid systems is bi-directional (see section on opioids) and is important not only for rewarding effects but also for withdrawal syndromes.
5. Neurobiological basis of withdrawal syndrome: Similar to opioids, cannabinoid withdrawal is associated with upregulation of cAMP pathway. But this occurs mainly in the cerebellum (an important region for movement coordination), which may account for milder somatic symptoms associated with cannabinoid as compared to opioid withdrawal. Motivational and emotional effects of cannabinoid withdrawal may be related to alterations in CRF function in limbic system (stress-like symptoms) and reduction in DA transmission (dysphoric and aversive effects).
6. Long-term adaptations: Very recent work suggests a role for endocannabinoids in synaptic plasticity in the reward circuitry. They are necessary for induction of LTD in the striatum and nucleus accumbens (Lovinger, Manzoni).

E. Ethanol and anxiolytics/sedatives
    1. Alcoholism is a complex disorder influenced by genetic, environmental and neurobiological factors. Withdrawal from chronic alcohol intake is accompanied by severe somatic symptoms. Alcoholism is characterized by chronic vulnerability to relapse after long after cessation of drinking.
    2. Ethanol has many physiological effects in brain, including influences on membranes, ion channels and multiple neurotransmitter receptors. Recent work has focused on the ability of ethanol to act as a positive allosteric modulator of $GABA_A$ receptors and a negative allosteric modulator of NMDA receptors.

Next page

However, as $GABA_A$ and NMDA receptors are highly expressed throughout reward circuitry, this doesn't help to identify potential sites of ethanol action within this circuitry. This has complicated studies of the neurobiology of ethanol addiction.

3. Role of DA systems in ethanol action: Activation of DA neurons is an important contributor to the reinforcing effects of ethanol. By enhancing $GABA_A$ receptor transmission in VTA, VTA GABA neurons are inhibited, which disinhibits the DA neurons. Ethanol may also directly excite DA neurons. After chronic ethanol exposure, adaptations apparently develop in mesolimbic DA function to offset excitatory effects of ethanol, such that withdrawal from chronic ethanol leads to decreases in DA cell activity and extracellular DA levels in nucleus accumbens. Drinking during withdrawal may be "motivated" by need to reverse DA deficits.
4. Role of other transmitter systems: Opioid systems also play an important role in the addictive actions of ethanol, as antagonists of _ and _ opioid receptors decrease ethanol consumption and reinforcement. Some effects of opioid systems may involve interactions with DA transmission in the nucleus accumbens. On the basis of animal studies, the opiate antagonist naltrexone has been used as a treatment for alcoholism. Recent work suggests that cannabinoid systems and neuropeptide Y may also be involved in ethanol reinforcement and consumption. Adaptations in CRF systems in the extended amygdala may contribute to anxiety and other affective changes in withdrawal.
5. Sedatives such as the barbiturates were used for the treatment of anxiety in the early in the 20^{th} century. Benzodiazepines were introduced in the early 1960's. Both drug classes have abuse liability, although less than stimulants and opiates. There is cross-tolerance and cross-dependence among ethanol, barbiturates and benzodiazepines, as all are positive allosteric modulators of $GABA_A$ receptors, and produce down-regulation of $GABA_A$ receptors after chronic treatment. Accordingly, benzodiazepines are commonly used, both in the clinic and on the street, to treat symptoms of alcohol withdrawal.

F. Nicotine
    1. Nicotine is responsible for reinforcing effect of tobacco products. Highly addictive - addiction results in 30% of those who experiment with tobacco products. One year after quitting, abstinence rate only 20%. Nicotine withdrawal syndrome is characterized by nicotine craving as well as dysphoria, anxiety, irritability, restlessness and increased appetite. Treated with nicotine replacement therapies, such as nicotine gum and patches, and/or with buproprion, a drug that is classified as an antidepressant but has multiple and complex effects in brain. Buproprion reduces craving in some smokers.
    2. Targets in brain: Nicotine is an agonist at the nicotinic acetylcholine receptor, an ionotropic receptor that passes sodium and calcium, leading to depolarization of target cells. Nicotine receptors are pentamers, composed of different combinations formed by 12 neuronal subunit gene products (_2- _10 and _2- _4). Of these, a subset is expressed in the VTA (_3-7 and _2-4). It is thought that _7 receptors form homomeric receptors; _3, _4 and _6 form heteromeric channels with _2 or _4; and _5 and _3 can associate with other _/_ pairs. Most VTA DA

Next page

neurons possess two types of _2 containing receptors, and include _4 as well as other subunits. About 40% of VTA DA neurons also express an _7 containing receptor.

3. Rewarding and addictive effects linked to activation of DA neurons in the ventral tegmental area: Studies in knockout mice implicate several subunits in the ability of nicotine to modulate DA neurons (_4, _6, _7, _2, _3) but suggest that _2 containing receptors play a critical role, as they necessary for nicotine-induced increases in DA release in VTA target areas and for nicotine self-administration. _2 containing receptors are present on DA and GABA cells in VTA, while _7 containing receptors are present on glutamate nerve terminals in VTA. A critical question is how nicotine produces rewarding effects given that high affinity nicotinic receptors, including the _2-containing receptors on DA and GABA cells of the VTA, are rapidly desensitized by blood nicotine levels attained during smoking. Initially nicotine excites DA neurons directly via activation of nicotinic receptors on DA cells and indirectly via activation of presynaptic _7 containing receptors that promote glutamate release. Excitation of GABA cells likely offsets this initial excitation to some degree. But within minutes, the _2 receptors on the DA cells and GABA cells desensitize. However, the _7 receptors desensitize to a lesser extent and continue to promote glutamate release, which now excites the DA cells even more effectively given the decrease in inhibitory GABA synaptic inputs. By enhancing glutamate release, presynaptic _7 receptors in VTA also promote LTP, providing a mechanism whereby nicotine may initiate synaptic plasticity in the VTA. This may contribute to long-term adaptations in the reward circuitry that underlie nicotine addiction. Consistent with demonstration that both NMDA and nicotinic acetylcholine receptor activation are required for development of nicotine-induced behavioral sensitization. Interestingly, both are also required for development of cocaine- and amphetamine-induced behavioral sensitization and nicotinic receptors are also implicated in cocaine's ability to produce conditioned place preference, another model for addiction. Makes sense in that acetylcholine projections (originating from mesopontine nuclei, PPT and LDT) are important regulators of VTA DA cell activity, thus cholinergic transmission likely to contribute to effects of other drugs of abuse.

III. Addiction and neuronal plasticity utilize common cellular mechanisms

A. An important current hypothesis is that adaptations leading to addiction involve the same glutamate-dependent cellular mechanisms that operate during learning and memory. In other words, addiction can be viewed as a form of neuronal plasticity – a very persistent form, as a high risk of relapse persists even after years of abstinence. This view of addiction is supported by several lines of evidence.
    1. Effects of chronic drug administration involve different circuits than acute drug reward – human and animal imaging studies suggest that brain regions implicated in learning and memory are activated during drug craving. Consistent with important role of conditioned responses and learned associations in drug craving.
    2. Glutamate, the key transmitter for neuronal plasticity, has been shown to play a key role in animal models of addiction (e.g., behavioral sensitization). Many

Next page

drug-induced adaptations require glutamate transmission for their development, whereas their expression is associated with altered glutamate transmission.

3. LTP and LTD may contribute to reorganization of neuronal circuits in both addiction and learning. For example, many drugs of abuse (and stress) have in common the ability to produce LTP in VTA DA neurons, producing a transient activation of DA neurons that is believed to trigger downstream adaptations that are more persistent. Drugs of abuse may influence LTP and LTD through PKA-dependent cascades that regulate glutamate receptor trafficking.
4. Studies at the cellular and molecular levels have demonstrated that common mechanisms are engaged during repeated drug administration and during learning, including common signal transduction cascades (e.g., protein kinase and phosphatase cascades, CREB, neurotrophic factors) and synaptic remodeling (changes in dendritic branching, spine density and number of branched spines).

B. Candidates for mediating persistent reorganization of neural transmission in addiction
    1. Changes in gene expression, leading to altered activity of neurons expressing these genes and ultimately to alterations in the activity of neuronal circuits. Two transcription factors are strongly implicated in addiction – CREB and ΔFosB. These factors mediate both homeostatic and sensitizing adaptations following repeated drug exposure. However, their levels return to normal after relatively short withdrawal periods (weeks-months). Thus, most likely that they are triggers for stable changes that occur through other mechanisms.
    2. Synaptic remodeling. Drugs of abuse (cocaine, amphetamine, morphine, nicotine) alter dendritic branching, spine density and spine branching in nucleus accumbens and prefrontal cortex. These effects are among the most long-lasting reported in response to chronic drug administration and are therefore good candidates for mediating its persistence. According to some theories, LTP is the first step in a cascade leading to structural changes in synapses. Thus drugs of abuse, by regulating LTP, may ultimately lead to synaptic remodeling. Drug-induced increases in neurotrophic factor expression may also contribute to alterations in dendritic morphology.
C. Challenge is to relate plasticity on cellular and molecular level to behavioral alterations that drive addiction (circuit level). For example, how do drug-associated cues acquire heightened ability to control behavior in drug addicts? Why are inhibitory control mechanisms impaired in addicts? If we identify pathways that are re-wired and know something about the pharmacology of systems that regulate specific pathways, perhaps pharmacological treatments can be devised to reduce craving and relapse.

Pain

Woolf, Costigan, Samad and Scholz

Define nociceptive, inflammatory functional and neuropathic pain and clinical physiological significance. Mention cancer pain as a composite of these syndromes

Identify mechanisms responsible for pain:

Transduction – nociceptor terminal
- Transduction receptor/ion channels TRPs/ASICs/P2x
- Peripheral sensitization Cox/Bradykinin/NGF PKA and PKC mediated phosphorylation/increased trafficking of receptor to terminal

Conduction primary sensory neuron/projection pathways
- Sensory neuron VGScs TTXs TTXR – local anesthetic action
- Ectopic excitability – VGSC, K channel – anticonvulsants/adrenergic receptor expression and sensitivity sympathetic drive

Transmission dorsal horn/brain stem/thalamus/cortex
- Excitation fast/slow glutamate/ATP/peptides
- Inhibition pre postsynaptic GABA/glycine/NA/Opioids local/descending

- Central sensitization early/late sickness syndrome
- Disinhibition

Perception
- Perceptual/cognitive/emotional/social/cultural element placebo/fMRI

Emphasize temporal features
- excitation *ms*
- use dependent plasticity postranslational modification/trafficking/internalization *seconds*
- transcriptional translational control phenotypic switches *days*
- structural sprouting cell death *months/years*

Genetic determinants
- Gender
- channelopathies

54. Magnetic Resonance Spectroscopy and Positron Emission Tomography

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INTRODUCTION

Brief history of MRS
Overview/scope of chapter

METHODS in MRS

1D-methods: pulse-acquire, spin-echo, J-editing, quantum-filters, decoupling
2D-methods: J-resolved echo

Single-voxel localization: PRESS, DRESS, STEAM, ISIS, LASER
Multi-voxel localization: CSI, HADAMARD, EPI

Time-domain fitting vs Frequency-domain Quantitation

BIOCHEMICAL AND PHYSIOLOGICAL MEASUREMENTS USING MRS

Proton (1H): membranes/neurodegeneration (NAA, choline)
glucose-metabolism (glutamine/glutamate)
energy-metabolism(pyrimidines, lactate)
neurotransmitter function (GABA, glx)

Phosphorus (31P): membrane-metabolism (phosphomonoesters, phosphodiesters)
energy-metabolism (inorganic phosphate, phosphocreatine, NTP)

Carbon-13 (13C): glucose-metabolism (glutamine, glutamate)

Sodium (23Na): intercellular vs extracellular Na concentrations

Lithium (3Li): 3Li-containing drug uptake

Flourine (19F): 19F-containing drug uptake

CLINICAL APPLICATIONS OF MRS

Studies of neuropsychiatric disorders: schizophrenia, depression, bipolar-disorders, Tourrette's Syndrome, autism, anxiety/panic disorders, dyslexia, substance-abuse/alcoholism, sleep disorders

Studies of neuropathological disorders: epilepsy, Alzheimer's, Parkinson's, multiple-sclerosis, stroke, cancer, mitochondrial dysfunction, brain-injury

Positron Emission Tomography

I. INTRODUCTION

A. In Vivo vs. In Vitro measures

1. Basic functions measured (metabolism, blood flow, blood volume, receptors, neurotransmitters)

II. METHODS

A. Radiotracers used for brain function

1. Single photon vs. positrons

2. Generator vs. cyclotron produced radioisotopes (including the maximum energy. range of particles, half-life or single/annihilation photons

III.DETECTION OF RADIOACTIVITY FOR BRAIN IMAGING

A. PET compared to SPECT

1. Crystals, reconstruction, correction for attenuation, scatter, randoms, etc.

B. ADVANTAGES AND DISADVANTAGES OF PET VS SPECT

C. RESOLUTION AND SENSATIVITIY OF PET/SPECT

1. Table and description of typical resolution sensitivity for PET/SPECT autoradiography, MRI, PET/SPECT

IV. FUNDAMENTALS OF RADIOTRACER METHODOLOGY

A. Basic radiochemistry for PET, SPECT- principals of labeling with radioisotopes and typical successful "ligands"

V. Validation of radiotracers

A. In Vitro vs. In Vivo rodent study

1. Typical validation for radiochemical and radiopharmaceutical purity.

VI. Role of Mathematical Modeling for Quantification

A. Differences Between Simple Tissue Time Activity Curve and Model Parameters with Examples, e.g., FDG, Glucose Metabolism, Blood Flow and Receptors Measures Of Binding Potential and Receptor Density

B. Limitation – Partial Volume Effect; Non-Specific Binding; Anatomical Vs. Functional Resolution; Ionizing Vs. Non-Ionizing Radiation and Risk to Subjects

VII. APPLICATIONS FOR BRAIN FUNCTION

A. THE SIMPLIST BRAIN FUNCTION (BLOOD VOLUME CEREBRAL BLOOD FLOW)

B. GLUCOSE AND OXYGEN MATABOLISM

1. The hexokinase step and principals of measuring the rate-limiting step as part of modeling.

C. NEURORECEPTOR IMAGING

1. Principals based *in vivo and in vitro* receptor binding and pharmacologic validation.

a) Quantification of receptors including saturation pharmacological competition studies

b)

VIII. CLINICAL APPLICATIONS

A. CNS DRUG DESIGN AND PRECLINICAL/CLINICAL DRUG DEVELOPMENT

1. **Investigation of receptor distribution / site of action**
2. **Effects of drugs on metabolism, blood flow and receptor binding**
3. **Estimating drug doses based on receptor occupancy**

IX. CLINICAL APPLICATIONS

A. CEREBRAL BLOOD FLOW VS. STROKE

1. **FDG and SPECT / Epilepsy**
2. **FDG/Cerebral Blood Flow and Cognitive Evaluation Studies**

X. NEUROPSYCHIATRIC APPLICATIONS

A. Neuroreceptor and FDG

B. Aging; Psychoses; Depression; Parkinson; Alzheimer's; Mental Retardation;

XI. SMALL ANIMAL PET/SPECT

A. Receptor Binding Role of knockout mice and future directions

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REFERENCES